Genetic Predisposition to Breast Cancer Due to Mutations Other Than \textit{BRCA1} and \textit{BRCA2} Founder Alleles Among Ashkenazi Jewish Women

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\textbf{IMPORTANCE} Among Ashkenazi Jewish women, 3 mutations in \textit{BRCA1} and \textit{BRCA2} severely increase the risk of breast and ovarian cancer. However, among Ashkenazi Jewish patients with breast cancer who do not carry one of these founder mutations, the likelihood of carrying another pathogenic mutation in \textit{BRCA1} or \textit{BRCA2} or another breast cancer gene is not known. This information would be valuable to the patient and family for cancer prevention and treatment.

\textbf{OBJECTIVE} To determine the frequency of cancer-predisposing mutations other than the \textit{BRCA1} and \textit{BRCA2} founder alleles among patients of Ashkenazi Jewish ancestry with breast cancer.

\textbf{DESIGN, SETTING, AND PARTICIPANTS} In this cohort study, genomic DNA of women from 12 major cancer centers with a first diagnosis of invasive breast cancer who identified themselves and all 4 grandparents as Ashkenazi Jewish and participated in the New York Breast Cancer Study (NYBCS) from 1996 to 2000 was sequenced for known and candidate breast cancer genes. Data analysis was performed from July 10, 2014, to March 10, 2017.

\textbf{MAIN OUTCOMES AND MEASURES} Genomic DNA from all 1007 NYBCS probands was sequenced for 23 known and candidate breast cancer genes using BROCA, a targeted multiplexed gene panel.

\textbf{RESULTS} Of the 1007 probands in the study, 903 probands had no founder mutations in \textit{BRCA1} or \textit{BRCA2}; of these probands, 7 (0.8\%) carried another pathogenic mutation in \textit{BRCA1} or \textit{BRCA2}, and 31 (3.4\%) carried a pathogenic mutation in another breast cancer gene (29 in \textit{CHEK2}, and 1 each in \textit{BRIPl} and \textit{NBN}). Of all inherited predispositions to breast cancer in the NYBCS, 73.8\% (104 of 142) were due to a \textit{BRCA1} or \textit{BRCA2} founder allele, 4.9\% (7 of 142) to another \textit{BRCA1} or \textit{BRCA2} mutation, and 21.8\% (31 of 142) to a mutation in another gene. Overall, 14.1\% (142 of 1007) of Ashkenazi Jewish patients with breast cancer in the NYBCS carried a germline mutation responsible for their disease: 11.0\% (111 of 1007) in \textit{BRCA1} or \textit{BRCA2}, and 3.1\% (31 of 1007) in \textit{CHEK2} or another breast cancer gene. Of the 111 patients with \textit{BRCA1} or \textit{BRCA2} mutations, 57 (51.4\%) had a mother or sister with breast or ovarian cancer and 54 patients (48.6\%) did not.

\textbf{CONCLUSIONS AND RELEVANCE} Comprehensive sequencing would provide complete relevant genetic information for Ashkenazi Jewish patients with breast cancer.

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Inherited loss-of-function mutations in BRCA1 (GenBank NM_007294) and BRCA2 (GenBank NM_000059) confer severe risks of breast and ovarian cancer on women who carry them. Knowing whether a patient with breast or ovarian cancer carries a cancer-predisposing mutation in BRCA1 or BRCA2 is valuable for both the patient and her family. The patient may be well served by targeted treatment,1,2 and as-yet unaffected sisters and daughters who learn that they also carry the mutation can undertake risk-reducing preventive strategies.3,4

Thousands of different cancer-predisposing mutations in BRCA1 and BRCA2 have been identified, and every population that has been evaluated harbors such mutations, nearly all individually extremely rare. In the Ashkenazi Jewish population, the mutation profile of BRCA1 and BRCA2 is distinctive, with the following 3 ancient founder mutations in these 2 genes: BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delIT. Notation for these variants based on Human Genome Variation Society conventions5 are NM_007294.3 (BRCA1)c.68_69delAG(p.Glu23Valfs), NM_007294.3(BRCA1):c.5266delUC(p.Gln1756Prolfs), and NM_000059.3(BRCA2):c.5946delIT(p.Ser1982Argfs). We will use the original names for the variants because they are more widely recognized. Combined, these 3 mutations are responsible for 10% of invasive breast cancer among Ashkenazi Jewish women.6,7

The relatively high frequency of the Ashkenazi Jewish founder mutations in BRCA1 and BRCA2 has enabled the effective use of cancer genetics services by Jewish women. However, for Ashkenazi Jewish patients with breast cancer who do not carry one of these 3 founder alleles, the chance of carrying some other pathogenic mutation in BRCA1 or BRCA2, or a pathogenic mutation in a different breast cancer gene, is not known. Should Ashkenazi Jewish women with breast or ovarian cancer who have negative results (ie, have wild-type sequences) for the 3 founder alleles obtain complete sequencing of BRCA1 and BRCA2 so as not to miss some other mutation? Should these Ashkenazi Jewish patients also be tested for mutations in other breast cancer genes?

We addressed these questions by sequencing all known breast and ovarian cancer genes in genomic DNA provided by participants of the New York Breast Cancer Study (NYBCS), a longstanding cohort of Ashkenazi Jewish women with a primary diagnosis of invasive breast cancer.8 Participants in the NYBCS were not selected for family history or age at diagnosis. Their genomic DNA had been evaluated for the founder mutations of BRCA1 and BRCA2, revealing one of these mutations in 104 of the 1007 probands. For the present project, we sequenced genomic DNA from these 1007 patients for all known breast cancer genes using our BROCA gene panel, then determined the frequency of cancer-predisposing mutations in BRCA1, BRCA2, and other breast cancer genes among patients with none of the founder mutations and with various family histories and ages at diagnosis.

Methods

Participants in the NYBCS were identified from 12 major cancer centers in the New York metropolitan area between 1996 and 2000, as previously described.5 Participants were women experiencing their first diagnosis of invasive breast cancer who identified themselves and all 4 grandparents as Ashkenazi Jewish. Eligible women were invited to participate regardless of age at diagnosis, family history, or prior genetic testing, which was still infrequent when these patients were enrolled. Patients provided pedigree information, permission to review records of pathologic findings for their breast cancer, and a blood sample for extraction of DNA. Of the 1007 index cases in the NYBCS, 987 (98.7%) requested information about their original genetic results and were provided this information by us in consultation with their hospital’s genetic counselors. Participants also gave consent for their DNA to be used for future studies of breast cancer genetics, as better sequencing technology became available. Some participants requested that their identifying information remain with their sample so that they or their family could be informed of results of future genetic testing; others agreed to the use of their DNA with basic risk factor information retained, but with their identifying information removed. The NYBCS was approved by the institutional review boards of the participating hospitals and by the University of Washington. Patients provided written informed consent.

For the present project, DNA extracted from blood was sequenced using BROCA, a targeted capture and massively parallel sequencing test developed at the University of Washington.8 For this project, we created a version of BROCA specifically targeting 23 established and candidate breast cancer genes: BRCA1, BRCA2, ATM (GenBank NM_000051), ATR (GenBank NM_001184), BAPI (GenBank NM_004656), BARD1 (GenBank NM_000465), BRIPI/FANCI (GenBank NM_032043), CDH1 (GenBank NM_004360), CHEK1 (GenBank NM_00114122), CHEK2 (GenBank NM_007194), FAM175A/ABRAXAS (GenBank NM_016067), FANCM (GenBank NM_020937), MRE11A (GenBank NM_055950), NBN (GenBank NM_002485), PALB2/FANCD1 (GenBank NM_024675), PTEN (GenBank NM_000341), RAD51B (GenBank NM_133509), RAD51C (GenBank NM_058216), RAD51D (GenBank NM_002878), RINT1 (GenBank NM_021930), SLX4/FANCP (GenBank NM_032444), TP53 (GenBank NM_000054), and 4 other genes.

Key Points

Question Among patients of Ashkenazi Jewish ancestry with breast cancer who do not carry one of the founder mutations in BRCA1 or BRCA2, what is the likelihood of carrying another cancer-predisposing mutation in BRCA1, BRCA2, or another breast cancer gene?

Findings In this cohort study, 1007 patients of Ashkenazi Jewish ancestry with breast cancer were evaluated by multiplex genomic sequencing for all known and candidate breast cancer genes. Among patients without a founder mutation in BRCA1 or BRCA2, 0.8% carried a different mutation in BRCA1 or BRCA2 and 3.4% carried a mutation in another gene.

Meaning Ashkenazi Jewish patients with breast cancer can benefit from genetic testing for all breast cancer genes.
**XRCC2** (GenBank NM_005431). Sequencing results were aligned to human reference genome hg19. Variants were identified after realignment of insertion-deletion variants (indels) and base quality recalibration. Single nucleotide variants, small indels, and copy number variants were identified as previously described.9 The consequences of mutations near splice junctions were tested in RNA isolated from patients’ blood. Missense mutations were included only if they were proven experimentally to be damaging, either as part of this project or previously. Data analysis was performed from July 10, 2014, to March 10, 2017. Allele frequencies were compared by 2-tailed χ² tests, Mantel-Haenszel tests for linear trend, or Fisher exact tests, as appropriate.

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Abbreviation: cDNA, complementary DNA.

### Results

The clinical characteristics for the NYBCS cohort are provided in **Table 1**. As previously reported,6 patients carrying one of the founder mutations in **BRCA1** or **BRCA2** were younger at diagnosis (mean [SD] age, 46.7 [10.7] years, vs 53.8 [11.1] years) and more likely to have a family history of breast or ovarian cancer (76 of 104 [73.1%]) than were patients with no founder mutation (519 of 903 [57.5%]).

Of the 903 patients with none of the 3 founder mutations in **BRCA1** or **BRCA2**, 7 (0.8%) carried a different pathogenic mutation in **BRCA1** or **BRCA2** and 31 (3.4%) carried a damaging...
mutation in another breast cancer gene (Table 2). Of the 7 mutations in BRCA1 or BRCA2, 1 (BRCA2 c.8635del5) has not been previously reported, and therefore may be private, and the other 6 have been reported as rare alleles in non-Jewish populations.10-12 Family history was suggestive for only 4 of the 7 BRCA1 or BRCA2 mutation carriers. The frequencies of these other BRCA1 and BRCA2 mutations were higher among patients diagnosed before 40 years of age (2 of 68 [2.9%]) compared with those diagnosed at 40 to 49 years of age (3 of 285 [1.1%]), 50 to 59 years of age (1 of 283 [0.4%]), or 60 years of age or older (1 of 267 [0.4%]) (Table 2). Of the 29 other mutations, 57 (51.4%) had a mother or sister with breast or ovarian cancer; of the 111 patients with a BRCA1 mutation, 46.4 (12.4) years for patients with a BRCA2 mutation; 52.6 (7.7) years for patients with a mutation in CHEK2, BRIP1, or NBN; and 53.9 (11.2) years for patients with no damaging mutation in any sequenced gene. Also, as expected, patients with a mother or sister with breast or ovarian cancer were more likely than those without such a family history to carry a damaging mutation in BRCA1 or BRCA2. However, approximately half of the patients with a damaging mutation in BRCA1 or BRCA2 had no close family history of breast or ovarian cancer of the 111 patients with BRCA1 or BRCA2 mutations, 57 (51.4%) had a mother or sister with breast or ovarian cancer and 54 (48.6%) did not. Also, of 31 patients with a damaging mutation in CHEK2, BRIP1, or NBN, 14 (45.2%) had a mother or sister with breast or ovarian cancer and 17 (54.8%) did not.

Figure 3 illustrates extended family R. Participant IV-7 was diagnosed with bilateral breast cancer at 48 years of age, with a recurrence at 59 years. She had negative test results for the BRCA1 and BRCA2 founder mutations, including BRCA2 6174delT, which had been identified in her cousin (IV-1). Sequencing the genomic DNA of participant IV-7 for all known breast cancer genes revealed that she is compound heterozygous for 2 mutations in CHEK2. All 3 of her sisters had also been

Integrating information from all genetic testing in the cohort reveals the distribution of mutations among genes (Figure 1) and the association among genotype, age at diagnosis, and family history (Figure 2). As expected, there is a strong association between age at breast cancer diagnosis and the likelihood of carrying a mutation in BRCA1 or BRCA2, whether a founder mutation or another damaging allele. However, age at diagnosis is not associated with the likelihood of carrying a damaging mutation in the other genes. The mean (SD) ages at diagnosis were 44.2 (9.9) years for patients with a BRCA1 mutation; 46.4 (12.4) years for patients with a BRCA2 mutation; 52.6 (7.7) years for patients with a mutation in CHEK2, BRIP1, or NBN; and 53.9 (11.2) years for patients with no damaging mutation in any sequenced gene. Also, as expected, patients with a mother or sister with breast or ovarian cancer were more likely than those without such a family history to carry a damaging mutation in BRCA1 or BRCA2. However, approximately half of the patients with a damaging mutation in BRCA1 or BRCA2 had no close family history of breast or ovarian cancer of the 111 patients with BRCA1 or BRCA2 mutations, 57 (51.4%) had a mother or sister with breast or ovarian cancer and 54 (48.6%) did not. Also, of 31 patients with a damaging mutation in CHEK2, BRIP1, or NBN, 14 (45.2%) had a mother or sister with breast or ovarian cancer and 17 (54.8%) did not.
Participant IV-7 was diagnosed with her first breast cancer at 48 years of age, despite testing negative for BRCA2 6174delT, which had been identified in her cousins IV-1 and IV-3. Sequencing by BROCA revealed IV-7 to be compound heterozygous for 2 mutations in CHEK2, one or both of which were also present in each of her 3 affected sisters. The young women in generation V who carry one of the family’s 3 mutations can be offered screening appropriate to their genotypes. Dark blue symbols indicate affected individuals; white symbols, unaffected individuals; light blue symbols, other cancers; a diagonal slash, known deceased individuals; BilBr, bilateral breast cancer; Br, breast cancer; N, normal allele; Pan, pancreatic cancer; Pr, prostate cancer; St, stomach cancer; and V, variant allele.

diagnosed with breast cancer, despite prior negative test results for the BRCA2 mutation of the family. Each sister also proved to carry 1 or both CHEK2 mutations. Homozygosity or compound heterozygosity for damaging alleles of CHEK2 is associated with breast cancer risk similar to that seen with BRCA1 or BRCA2. All daughters of the compound heterozygous sisters inevitably carry one of the CHEK2 mutations. Surveillance for these daughters will be more frequent than for a young woman whose mother had breast cancer with no genetic predisposition.
Discussion

Many Ashkenazi Jewish patients with breast cancer have been tested for the founder mutations of \(BRCA1\) and \(BRCA2\). If a patient is negative (ie, has a normal sequence) for these mutations, should she and her physician consider additional testing? Our results offer perspectives on this question. First, for an Ashkenazi Jewish patient with breast cancer who does not carry a founder mutation in \(BRCA1\) or \(BRCA2\), the chance of carrying a different, equally damaging mutation in \(BRCA1\) or \(BRCA2\) is about 1%. If she was diagnosed before 40 years of age, this chance increases to about 3%. Patients with such mutations should be counseled for preventive salpingo-oophorectomy and may be considered for poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitor therapy. Their mutations also offer an opportunity for testing and cancer prevention for daughters and sisters. However, a likelihood of 1%, or even 3%, may be below the threshold of consideration for additional testing for most patients. Second, the chance that an Ashkenazi Jewish patient with breast cancer and no \(BRCA1\) or \(BRCA2\) founder mutation carries a damaging mutation in \(CHEK2\) or another moderate penetrance gene is 3% to 4%. Most of these mutations are associated with a 2-fold increase in risk of breast cancer and no increase in risk of ovarian cancer,13 so they are not likely to affect the treatment of a patient already under care for her breast cancer.

On the other hand, family R (Figure 3) offers an extreme example of the value of genotyping beyond the 3 founder alleles. The lesson of family R is that if multiple cases of breast cancer in a family remain unresolved by the mutation of the proband, then comprehensive sequencing is strongly suggested to identify other causal mutations. The identification of \(CHEK2\) mutations in family R likely did not alter treatment for the patients already diagnosed with breast cancer, but it was highly informative for the daughters of these patients. The most recent National Comprehensive Cancer Network guidelines recommend that cancer-free carriers of mutations in \(CHEK2\) and other moderate penetrance genes undertake annual mammography or breast magnetic resonance imaging with contrast beginning at 40 years of age4 and that they be aware of a moderate increase in the risk of colon cancer.15 These recommendations are germane for the young women of family R who carry a \(CHEK2\) mutation.

Many healthy, cancer-free Ashkenazi Jewish women have been tested for the Ashkenazi Jewish founder mutations of \(BRCA1\) and \(BRCA2\), with negative (ie, normal) results. Should these cancer-free women be tested again to identify any other mutations? The chance that an Ashkenazi Jewish patient with breast cancer harbors a nonfounder mutation in \(BRCA1\) or \(BRCA2\) is less than 1%; therefore, the chance that a cancer-free Ashkenazi Jewish woman harbors such a mutation is much less than 1%. Based on the results of a previous study,13 the chance that a cancer-free Ashkenazi Jewish woman carries \(CHEK2\) p.S284F is 1.4%; therefore, the chance that a cancer-free Ashkenazi Jewish woman carries any \(CHEK2\) mutation, with a corresponding 2-fold increased risk of breast cancer, is approximately 1.7%. For cancer-free Ashkenazi Jewish women with no founder mutation in \(BRCA1\) or \(BRCA2\) who are particularly concerned with remaining genetic risk, comprehensive genetic testing with a multigene panel would identify all \(CHEK2\) mutations, as well as private mutations in any other gene.

An additional consideration for genetic testing for Ashkenazi Jewish women is the evolution of admixture in Ashkenazi Jewish populations. In the New York Ashkenazi Jewish population of the present study, the contribution of founder alleles to the risk of breast cancer was very strong: 128 of 142 patients (90.1%) with a mutation in any gene carried an Ashkenazi Jewish founder allele, whether in \(BRCA1\), \(BRCA2\), or \(CHEK2\). The relative importance of founder vs nonfounder mutations reflects both the antiquity and the historic endogamy of this population. The median birth year of the participants in the NYBCS was 1940. It will be important to keep changing marriage patterns in mind when considering genetic testing for future generations of Jewish women, whose ancestries may be more admixed than the ancestries of their grandmothers.

These considerations suggest that Ashkenazi Jewish women who have not yet been tested for any mutations in any breast cancer gene be offered comprehensive testing for all mutations in all genes. Given that complete sequencing of all breast cancer genes is now straightforward and inexpensive, its use as the primary testing tool offers a uniform approach for women of all ancestries and precludes the need to consider additional testing for Ashkenazi Jewish women with negative results for only the \(BRCA1\) and \(BRCA2\) founder alleles.

Limitations

There are 2 limitations to this study. First, because probands were ascertained for a diagnosis of breast cancer, only genes known or suspected to harbor mutations increasing the risk of breast cancer were sequenced. Genes that harbor mutations predisposing to cancers other than breast, such as genes for Lynch syndrome, were not sequenced. Second, the BROCA panel enables detection of all mutations in coding regions, untranslated regions, or introns of all targeted genes, but does not include sequence for still-identified distant regulatory regions of these genes. Identification of mutations in distant regulatory regions of cancer genes is an important next step in genomic analysis of inherited predisposition to cancer.

Conclusions

Among NYBCS participants, approximately half of the patients with a damaging mutation in any breast cancer gene did not have a family history suggesting inherited predisposition. Mutations in these families were likely inherited from fathers, and the combination of small family size and chance in genetic transmission yielded few female relatives carrying mutant alleles. Therefore, to limit genetic testing to patients with a suggestive family history is to miss about 50% of patients with actionable mutations. The most recent national screening guidelines recommend genetic testing for all Ashkenazi Jewish patients with breast cancer.4 This recommendation is fine, but testing women only after they develop cancer severely lim-
its the power of precision medicine. To discover a mutation only after cancer is diagnosed is a missed opportunity to have prevented that cancer. Many of these cancers could be prevented by offering genetic testing as described here to all women before they develop breast cancer, as part of routine medical care.\textsuperscript{16}

**ARTICLE INFORMATION**

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**Study concept and design:** Walsh, King.
**Acquisition, analysis, or interpretation of data:** All authors.
**Drafting of the manuscript:** Gulsuner, Lee, King.
**Statistical analysis:** Gulsuner, Lee, King.
**Obtained funding:** King.
**Administrative, technical, or material support:** Walsh, Mandell, Casadei, Lee, King.
**Study supervision:** King.

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**REFERENCES**